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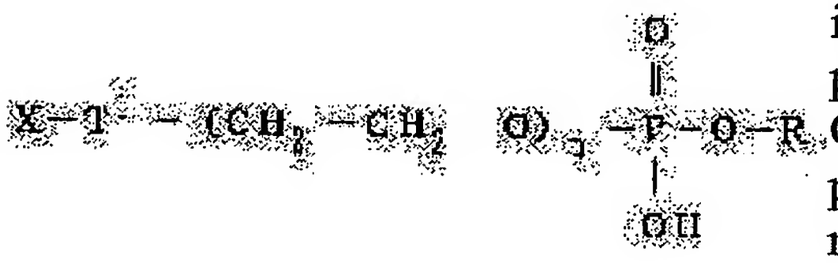
(54) PHOSPHOLIPID AND LIPOSOME

(57)Abstract:
PURPOSE: To provide a new phospholipid having a structure consisting of a monosaccharide or an oligosaccharide bonded to a phosphoric acid lipid ester through a polyoxyethylene group an useful e.g. for the modification of liposome drug carrier for imparting the liposome with directivity to prescribed organ.

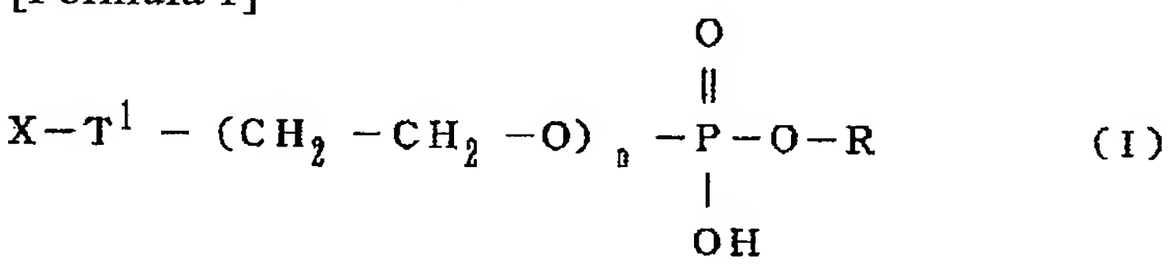


CONSTITUTION: The objective phospholipid expressed by formula (X is monosaccharide residue, oligosaccharide residue, etc.; T1 is O NHCO, OCO, etc.; R is cholesterol residue, 12-20C straight-chain alkanol residue, etc.; (n) is 1-8) and useful e.g. for the modification of liposome for drug carrier is produced by adding ethylene glycol monobenzyl ether and methylene chloride to ß-D-galactose pentaacetate, cooling the obtained solution with ice, adding BF3 diethyl ether complex to the solution, reacting the components, adding 10% Pd-carbon,

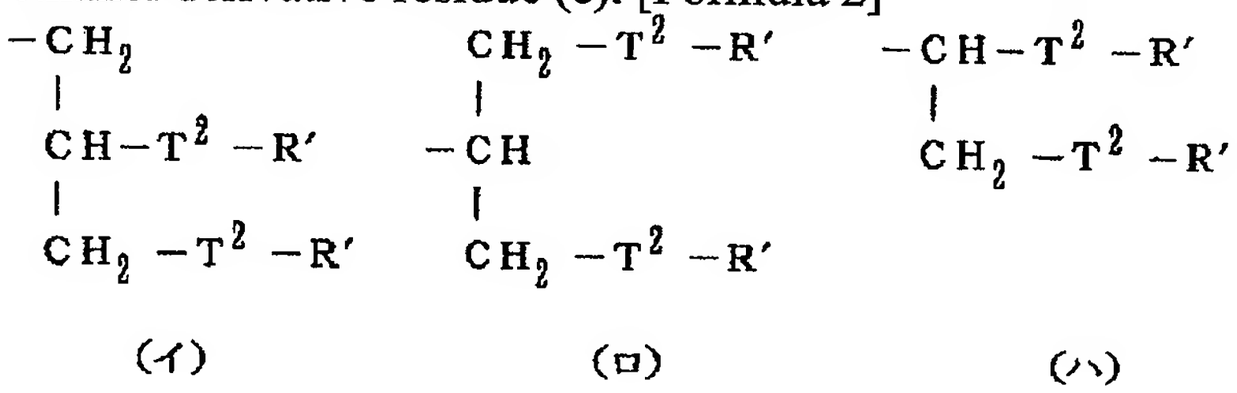
subjecting to catalytic reduction under atmospheric pressure, removing the catalyst from the product, adding 2-cyanoethyl N,N-diisopropyl chlorophosphoramidite and diisopropylethylamine and reacting with 2-(n- hexadecyl)-1-octadecanol, etc.

CLAIMS

[Claim(s)]
[Claim 1] Phospholipid expressed with the following general formula (I).
[Formula 1]



X among the above-mentioned formula A glucose, a deoxy glucose, a mannose, a galactose, A fucose, a ribose, a deoxyribose, a rhamnose, a xylose, Arabinose, an ERIS sirloin, a sialic acid, a uronic acid, and one monosaccharide of the hexosamines, O-alkyl derivative containing O- of these monosaccharides or N-acyl derivative, and a carboxy alkyl derivative and a phosphoric acid, or one monosaccharide derivative of the sulfates, Or it is the oligosaccharide which uses these monosaccharides and/or a monosaccharide derivative as composition sugar. - They are (O) CO-, -NHCOO-, -OOCNH-, or -NHCONH-. T1- -O-, -NHCO-, -OCNH-, and - OC(O)- and - R They are a cholesterol residue, the straight chain alkanol residue of the carbon atomic numbers 12-20, the following propanol derivative residue (b), a (b), or the following ethanol derivative residue (c). [Formula 2]



these residues -- setting -T2- -O-, -NHCO-, -OCNH-, and - OC(O)- and - it is (O) CO-, -NHCOO-, -OOCNH-, -NHCONH-, or -CH2-, R' is the straight chain alkyl group of the carbon atomic numbers 12-20, and n is the integer of 1-8
[Claim 2] The liposome characterized by containing the phospholipid expressed with the above-mentioned general formula (I).

DETAILED DESCRIPTION

[0001]

[Industrial Application] this invention relates to the liposome which has the internal-organs directivity embellished by the phospholipid and such phospholipid which embellish the liposome to which the use as a medicine carrier is expected, and can give the directivity to predetermined internal organs to a liposome.

[0002]

[The conventional technology and a trouble] The liposome is expected as a carrier when prescribing a medicine for the patient as stated to editing "a liposome" (Nankodo Co., Ltd.) besides Nojima. Although various attempts are made that it should improve so that it may have internal-organs directivity so that such a liposome may shift with the priority to desired internal organs namely, the result with which it can be satisfied of all enough is not obtained.

[0003] this invention person has inquired paying attention to sugar as a homing device required to embellish a liposome and give internal-organs directivity or an internal-organs recognition element. However, although it is necessary to consider as the lipid derivative since a liposome is embellished as known well when using sugar as an internal-organs recognition element, even if in a certain case the lipid derivative of sugar is stabilized and cannot embellish a liposome, and in a certain case it is stabilized and can embellish a liposome, sugar may not function as an internal-organs recognition element.

[0004]

[Means for Solving the Problem] As a result of this invention person's performing various examination to the bottom of the background of such conventional technology, when having introduced sugar into the phosphoric ester which has a fat-soluble basis in a molecule on both sides of ethylene glycol or a polyethylene glycol, it knew that the lipid derivative which is stabilized and can embellish a liposome regardless of the kind of sugar is obtained, and various sugar will function as an expected internal-organs recognition element, and this invention completed based on such knowledge. Although a diacylglycerol phosphoric acid or its derivative was incidentally used since a liposome was prepared or embellished conventionally, it is not known that the compound of this invention will use for the use of this invention.

[0005] That is, this invention relates to the liposome to which the internal-organs directivity which has sugar as an internal-organs recognition element, and which was embellished by new phospholipid and such phospholipid was given.

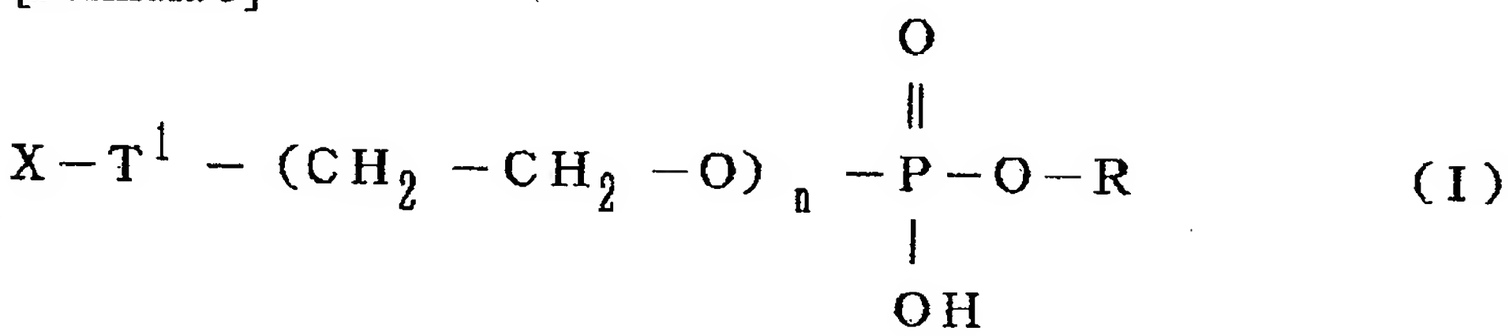
[0006] Hereafter, this invention is serially explained to a detail.

[0007] The new phospholipid of this invention is explained [1st].

[0008] The phospholipid of this invention is expressed with the following general formula (I).

[0009]

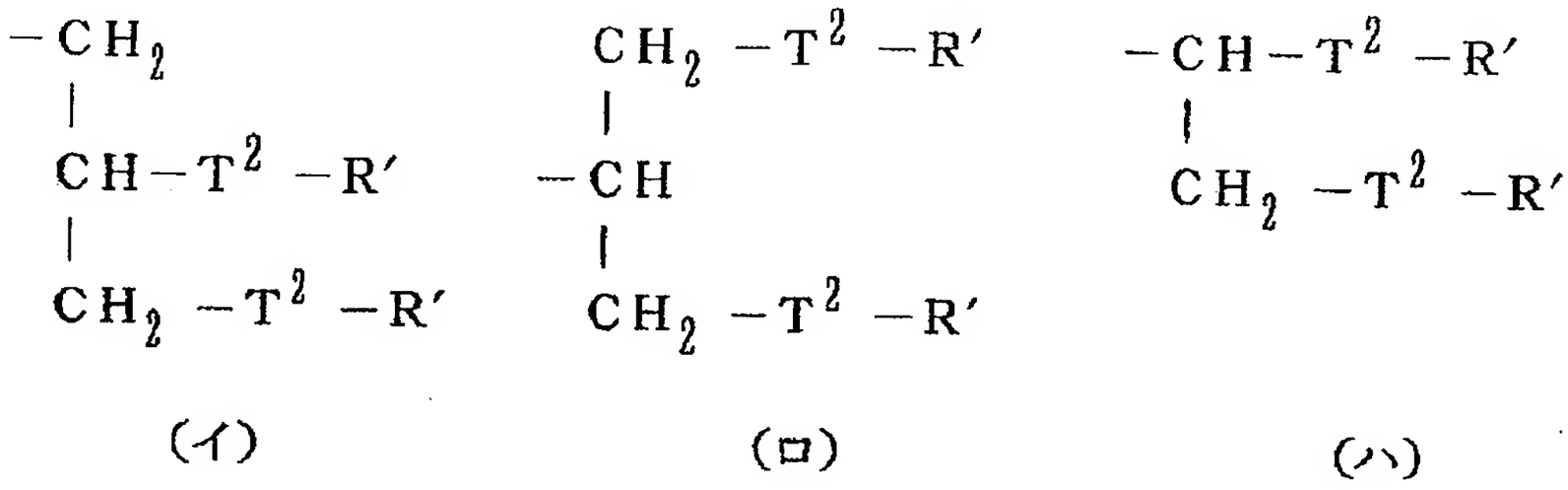
[Formula 3]



(I)

[0010] X among the above-mentioned formula A glucose, a deoxy glucose, a mannose, a galactose, A fucose, a ribose, a deoxyribose, a rhamnose, a xylose, Arabinose, an ERIS sirloin, a sialic acid, a uronic acid, and one monosaccharide of the hexosamines, O-alkyl derivative containing O- of these monosaccharides or N-acyl derivative, and a carboxy alkyl derivative and a phosphoric acid, or one monosaccharide derivative of the sulfates, Or it is the oligosaccharide which uses these monosaccharides and/or a monosaccharide derivative as composition sugar. - They are (O) CO-, -NHCOO-, -OOCNH-, or -NHCONH-. T1- -O-, -NHCO-, - OCNH-, and - OC(O)- and - R It is a cholesterol residue, the straight chain alkanol residue of the carbon atomic numbers 12-20, the following propanol derivative residue (b), a (b), or the following ethanol derivative residue (c), and is [0011].

[Formula 4]



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[0012] these residues -- setting -T2- -O-, -NHCO-, -OCNH-, and - OC(O)- and - it is (O) CO-, -NHCOO-, -OOCNH-, -NHCONH-, or -CH2-, R' is the straight chain alkyl group of the carbon atomic numbers 12-20, and n is the integer of 1-8

[0013] As a uronic acid as X in the above-mentioned formula, a GARAKU TRON acid, glucuronic acid, a MANSURON acid, etc. can be mentioned, and a glucosamine, a mannosamine, a galactosamine, etc. can be mentioned as a hexosamine.

[0014] As for O- of a monosaccharide, or the carbon atomic number of the acyl group of N-acyl derivative, 1-4 are desirable. A monosaccharide is acylated by the

conventional method and such an acyl derivative can also be obtained, although what exists in nature, such as 1-methyl glucose and N-acetyl mannosamine, is known.

[0015] As for the carbon atomic number of the alkyl group of O-alkyl derivative of a monosaccharide, 1-4 are desirable. A carboxy alkyl derivative is also contained in O-alkyl derivative. The method more nearly special than a monosaccharide as a method of obtaining such an O-alkyl derivative is not required.

[0016] The phosphoric acid or sulfate of a monosaccharide is obtained by introducing a phosphoric acid or a sulfuric acid into a sialic acid, a uronic acid, or the carboxyl group of a monosaccharide by which carboxy alkylation was carried out by carrying out ester combination. The method by which the method of obtaining such ester combination is also learned well is applicable. the oligosaccharide which uses a monosaccharide or a monosaccharide derivative as composition sugar -- the thing of a monosaccharide and/or a monosaccharide derivative which consists of 2-4 pieces preferably -- it is -- the sugar of an end -- the hydroxyl group of the anomer grade -- which hydroxyl group of the 2nd sugar, and alpha -- or beta combination of is done

[0017] T1 Although any are sufficient as the hydroxyl group by the side of sugar when it is ether linkage, the ester combination with the hydroxyl group by the side of sugar, or a urethane bond, when it is ether linkage, the hydroxyl group of anomer grade is easy for a synthetic reaction. Such ether linkage, a urethane bond, or ester combination can also be obtained by the conventional method.

[0018] T1 The carboxyl group at the time of being the acid-amide combination with the carboxyl group of sugar or ester combination is a carboxyl group of the carboxy acylation derivative of a sialic acid, a uronic acid, or a monosaccharide. These acid-amides combination and an ester ligation reaction are good by the usual method.

[0019] T1 Although the amino group of a hexosamine is usually used, one of the hydrogen atom of the acyl group of the acyl of a monosaccharide or an alkyl derivative or an alkyl group has replaced the amino group at the time of being the acid-amide combination with the amino group of sugar, a urethane bond, or urea combination by the amino group, and it may be the amino group. Such acid-amide combination, a urethane bond, and urea combination are also obtained using the usual reaction.

[0020] the portion of -(CH2-CH2-O) n- in a formula (I) -- a spacer -- calling -- T1 ******** -- it states in more detail

[0021] When combination with sugar and a spacer is acid-amide combination, under a dehydration condensation condition, under existence of a suitable catalyst (for example, an N-hydroxysuccinimide, N, and N'-dicyclohexylcarbodiimide, a 1-hydroxy benzotriazol), a raw material compound can be made to be able to react for 1 to 24 hours, and can be obtained with the reaction temperature of 0 degree C - a room temperature in the solvent (for example, an acetonitrile, a dimethylformamide, a methylene chloride, an ethylene chloride) which does not specifically participate in a

[0022] Moreover, when combination is ester combination, under a dehydration condensation condition, under existence of a suitable catalyst (for example, an N-

hydroxysuccinimide, N, and N'-dicyclohexylcarbodiimide, a 1-hydroxy benzotriazol), a raw material compound can be made to be able to react for 1 to 24 hours, and can be obtained with the reaction temperature of 0 degree C - a room temperature in the solvent (for example, an acetonitrile, a dimethylformamide, a methylene chloride, an ethylene chloride) which does not specifically participate in a reaction.

[0023] Furthermore, when combination is ether linkage, in the solvent (for example, a dimethylformamide, a tetrahydrofuran) which does not participate in a reaction, with room temperature -100 degree C reaction temperature, the hydroxyl group of sugar or the hydroxyl group of a spacer can make that by which replaced or the tosylation was carried out to the halogen atom able to react for 1 to 48 hours, and it can obtain it.

[0024] the solvent (for example, the ether and a tetrahydrofuran --) which does not participate in a reaction what used the amino group of a raw material compound, and the hydroxyl group of other raw material compounds as the chloro formylation object according to the conventional method (for example, it processes by 1 and 1-carbonyldiimidazole) further again when combination is a urethane bond With the bottom of existence of a catalyst (for example, bases, such as a triethylamine and a sodium hydrogencarbonate) suitable in 1 and 4-dioxane, and the reaction temperature of 0 degree C - a room temperature It can be made to be able to react for 0.5 to 24 hours, and can obtain.

[0025] When combination is urea combination, under existence of the solvent (for example, the ether, a tetrahydrofuran, benzene, toluene, ethanol) which does not participate in a reaction, with the reaction temperature of room temperature - 100 **, what isocyanate-ized the amino group of a raw material compound and the amino group of other raw material compounds according to the conventional method (for example, it processes by the phosgene) can be made to be able to react for 1 to 24 hours, and can be obtained further again.

[0026] T1 The time of being a glycosidic linkage is described still in detail. That is, such combination is (a). It can obtain by making the halogenation sugar by which the hydroxyl group of the anomer grade of sugar was replaced with the halogen, and the hydroxyl group of a spacer react under existence of an activator (mercury salts, such as silver salt, such as a silver silicate, a silver carbonate, perchloric acid silver, and silver trifluoromethane sulfonate, and a mercury oxide, tin salt) in the solvent (for example, a dichloroethane, a methylene chloride, benzene, toluene) which does not participate in a reaction. In addition, when bromine-ized sugar processes the sugar by which the hydroxyl group was acetylated with a hydrogen bromide/acetic acid, fluoride sugar can be obtained again, when the hydroxyl group of anomer grade processes non-protected sugar by diethylamino sulphato RIFURUORORAIDO.

[0027] Moreover, (b) The sugar which the hydroxyl group acylated, and a spacer (what has a hydroxyl group) can be obtained also by making it react in the solvent (for example, a methylene chloride, a dichloroethane) which does not participate in a reaction under existence of acid catalysts (for example, a boron trifluoride and the diethylether complex (BF3 and Et2 O), trimethylsilyl trifluoromethane sulfonate (TMSOTf), pilus JIUMUPARA toluenesulfonic acid (PPTS), etc.).

[0028] Furthermore, (c) The hydroxyl group of the anomer grade of sugar non-protected sugar Bases, such as 1, 8-diazabicyclo (5, 4, 0)-7-undecene (DBU), and potassium carbonate, It is the above (b) under existence (for example, BF3 and Et2 O, TMSOTf, PPTS, etc.) of the acid catalyst after processing by the TORIKURORO acetonitrile and considering as imidate. If it can set, on the same conditions, it can be made to be able to react with a spacer (what has a hydroxyl group), and can obtain.

[0029] It is (d) further again. The sugar and the spacer (what has a hydroxyl group) from which the hydroxyl group was changed into the alkyl thio machine can be performed also by making it react under existence (for example, N-iodine succinimide (NIS) / trifluoromethane sulfonic acid (TfOH)) of an activator.

[0030] You may make it combine with the spacer which has not been probably combined with a phosphoric acid, or sugar may introduce sugar into a reactant with the ester derivative (that by which after-mentioned "lipid" was introduced into the phosphoric acid) of a spacer, a phosphoric acid, or a phosphoric acid. In the case of the former, of course, you have to introduce a phosphoric acid or its derivative into the reactant of sugar and a spacer further. Moreover, the specified substance can also be obtained through the post-oxidization and the deprotection in which a phosphorous acid derivative and ester combination were made to form.

[0031] A spacer has the functional group, i.e., the hydroxyl group, amino group, or carboxyl group for combining with sugar at the end, and the other end has a hydroxyl group for forming a phosphoric acid and ester combination. In other words, ethylene glycol, a polyethylene glycol, or the hydroxyl group of those ends is replaced by the amino group or the carboxyl group.

[0032] The ligation reaction with a spacer, a phosphoric acid, or its ester derivative is possible by the in general known method. However, it is simple to be based on the force fall aminodite method which goes via phosphorous acid triester.

[0033] When R (it may be hereafter called a "lipid") in a formula (I) is a cholesterol residue, the hydroxyl group of cholesterol can use for the ester combination with a phosphoric acid as it is. Although the carbon atomic number is 12-20 when R is a straight chain alkanol residue, it is 14-18 more preferably.

[0034] Although a carbon atomic number is the thing of 12-20 also in the straight chain alkyl group of R', the thing of 14-18 is more desirable.

[0035] The combination with a phosphoric acid and a lipid is obtained by the ester reaction of the thing and lipid which the phosphoric acid itself or the phosphoric acid, and the spacer (or thing which sugar combined with the spacer) combined. There is especially no point that this ester ligation reaction changes with the ester ligation reaction of the aforementioned spacer and a phosphoric acid.

[0036] The phospholipid of this invention obtained in this way can give the directivity to the internal organs to a liposome, when it has the receptor with which it is stabilized, and a liposome can be embellished and internal organs can recognize the sugar of phospholipid to be.

[0037] The liposome of this invention is explained [2nd].

[0038] The liposome of this invention is a liposome which blended the phospholipid which is matter of this invention mentioned above, and is an object which uses the specific property of this matter chiefly.

[0039] That what is necessary is for there to be no limit special to the others which use the phospholipid of this invention in manufacture of the liposome of this invention, and just to perform it to it according to a well-known method conventionally, fundamentally, with other membrane components which are amphiphiles, it dissolves or distributes and the phospholipid of this invention is mixed to a solvent. Specifically, membrane component matter, such as lipids, such as a phospha CHIJIRU choline, a sphingomyelin, and a phospha CHIJIRU ethanolamine, and a dialkyl type composition surfactant, and the phospholipid of this invention are mixed beforehand, and the water dispersion of a liposome is prepared for this according to a well-known method (Ann.Rev.Biophys.Bioeng., 9, 467 (1980)). This liposome may contain antioxidants, such as electric charge matter, such as sterols, such as cholesterol, a dialkyl phosphoric acid, and a stearyl amine, and a tocopherol, as a film stabilizing agent.

[0040] In the liposome prepared as mentioned above, it is desirable about 1 / to make preferably into 1/20 or more mole ratios 40 or more mole ratios of rates for which the matter of this invention accounts to all lipid membrane components.

[0041] There is especially no limit in the medicine which this liposome can hold, and the physiological active substance represented by the anticancer agent which a water-soluble medicine or a lipophilicity medicine is sufficient as, for example, is represented by cytosine arabinoside, a daunorubicin, and the methotrexate, the antibiotic represented by penicillin G, an insulin, interferon, and the organization plasminogen activator can be mentioned.

[0042]

[Example] Hereafter, an example and the example of inspection explain this invention further.

[0043] Example 1 (refer to composition of a compound 4-5, and drawing 1)

(a) Synthetic glycolic-acid sodium of a compound 4-1 40ml [of N.N-dimethylformamide] and benzyl bromide 6.12ml was added to 5.048g, and it agitated at 80 degrees C under argon atmosphere for 17 hours. The solvent was distilled off under reduced pressure, ethyl acetate was added to the residue, and insoluble matter was ****(ed). A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl acetate 3:1), and let the specified substance be colorless oily matter. 7.738g was obtained.

[0044] 1 H-NMR(delta and CDCl3): 2.38 (t, 1H, J= 5.5Hz), 4.20 (d, 2H, J= 5.5Hz), 5.24 (s, 2H), and 7.33-7.40 (m, 5H).

[0045] IR(KBr tab): 1744cm-1.

[0046] (b) Synthetic beta-D-galactose of a compound 4-2 PENTA acetate Compound 4-1 2.797g (1.3eq) and 50ml of methylene chlorides were added and melted to 5.060g, little "molecular-sieve 4A" was added, and it agitated for 50 minutes at the room temperature. This was ice-cooled, and, in addition, 6.38ml of boron-trifluoride diethylether complexes was melted and agitated at the room temperature for 13 hours to 10ml of methylene chlorides. Insoluble matter was ****(ed), it diluted with the methylene chloride, and saturation brine washed 6 times. The organic layer was dried on magnesium sulfate and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:1), and they are the specified substance and a beta-D-galactose. Let mixture (mole-ratio; about 2:1) of PENTA acetate be colorless oily matter. 3.312g was obtained.

[0047] (c) The compound 4-2 and beta-D-galactose of the synthetic above of a compound 4-3 Mixture of PENTA acetate 3.312g was melted to 100ml of ethyl acetate, Pd-C (dry) 0.105g was added here 10%, and catalytic reduction was carried out by the ordinary pressure for 1.5 hours. The catalyst was ****(ed) and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; chloroform-methanol-water 60:35:7), and let the specified substance be a colorless amorphous substance. 1.907g was obtained.

[0048] 1 H-NMR(delta, DMSO-d6): 1.92 (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 2.11 (s, 3H), 3.85 (s, 2H), 4.04 (d, 2H), 4.14 (brt, 1H), 4.79 (d, 1H, J= 8.1Hz), 4.95 (dd, 1H, J= 8.1Hz, 10.4Hz), 5.14 (dd, 1H, J= 10.4Hz, 3.5Hz), and 5.25 (brd).

[0049] IR(KBR tab): 1751cm-1.

[0050] [alpha] D 24=-7.5 degree (c= 0.98, MeOH).

[0051] (d) The synthetic compound 4-3, 0.368 g, and the 1-hydroxy benzotriazol of a compound 4-4 0.154g is melted to 5ml of ethyl acetate, and it is an N and N'-dicyclohexylcarbodiimide here. 0.203g was added and it agitated at the room temperature for 2.5 hours. Precipitation was ****(ed) and the solvent was distilled off under reduced pressure. It used for the following reactions, without refining it, using this as activity ester.

[0052] 1, 2-O, and O-JIHEKISA desyl-rac-glycero-3-phosphoethanolamine 5ml of methylene chlorides was made to suspend 0.300g, the above-mentioned activity ester whole quantity was melted here at 5ml of methylene chlorides, the solution set to pH=9 by the triethylamine was added, and it applied to the ultrasonic wave for 30 minutes. After ice-cooling reaction mixture and being referred to as pH=1 with 1-N hydrochloric acid, the solvent was distilled off under reduced pressure. After removing water with azeotropy with benzene and ethanol, the residue was refined in the "Sephadex LH-20" column (resin; about 150ml, elution solvent; chloroform-methanol 1:1), and the specified substance was made into the colorless amorphous substance, and was obtained 0.415g.

[0053] 1 H-NMR(delta, CD3 OD): 0.89 (t, 6H, J= 7.0Hz), 1.25- 1.38 (m, 52H) and 1.57 (quintet, 4H, J= 6.8Hz) -- 1.99 (s, 3H), 2.05 (s, 3H), 2.12 (s, 3H), 2.18 (s, 3H), 3.45-3.66 (m, 9H), 3.88-3.96 (m, 4H), 4.10 (br t, 1H) 4.14-4.21 (m, 2H), 4.17 (d, 1H,

J= 15.1Hz) 4.29 (d, 1H, J= 15.1Hz), 4.73 (d, 1H, J 1, 2 = 7.6Hz), 5.14 (dd, 1H, J= 10.4Hz, 3.2Hz), 5.19 (dd, 1H, J= 7.6Hz, 10.4Hz), 5.42 (dd, 1H, J= 3.2Hz, 1.0Hz).

[0054] IR(KBR tab): 1755cm-1.

[0055] [alpha] D 28=-1.4 degree (c= 0.94, CHCl3-MeOH 1:1).

[0056] (e) Benzene 3ml and methanol 3ml were added and melted to the synthetic compound 4-4 of a compound 4-5, and 0.379 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated for 30 minutes. It ice-cooled, and after adding 1-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. 0.274 g After removing water with azeotropy with benzene and ethanol, the residue was refined in the "Sephadex LH-20" column (resin; about 150ml, elution solvent; chloroform-methanol-water 65:15:1), and the specified substance was made into the colorless amorphous substance, and was obtained.

[0057] 1 H-NMR(delta, CD3 OD): 0.89 (t, 6H, J= 7.0Hz), 1.24- 1.39 (m, 52H) and 1.57 (br quintet, 4H) -- 3.45-3.67 (m, 12H), 3.75 (dd, 1H, J5, 6a=5.4Hz, J6a, 6b =11.5Hz), 3.80 (dd, 1H, J= 6.6Hz, 11.5Hz) 3.89 (br d, 1H), 3.94-4.07 (m, 4H), 4.16 (d, 1H, J= 15.9Hz), 4.28 (d, 1H, J= 7.6Hz), 4.33 (d, 1H, J= 15.9Hz).

[0058] IR(KBr tab): 1659cm-1.

[0059] [alpha] D 29=-3.5 degree (c= 1.04, CHCl3-MeOH 1:1).

[0060] FAB-MS: [M+H] + ; m/z=885.

[0061] Example 2 (refer to composition of a compound 4-9, and drawing 2)

(a) Synthetic beta-D-galactose of a compound 4-6 PENTA acetate Ethylene glycol monochrome benzyl-ether 2.38ml and 50ml of methylene chlorides were added and melted to 5.024g, little "molecular-sieve 4A" was added, and it agitated for 50 minutes at the room temperature. This was ice-cooled, and, in addition, 6.33ml of boron-trifluoride diethylether complexes was melted and agitated at the room temperature for 13.5 hours to 10ml of methylene chlorides. Insoluble matter was ****(ed), it diluted with the methylene chloride, and saturation brine washed 6 times. The solvent which dried the organic layer on magnesium sulfate was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 2:1), and they are the specified substance and a beta-D-galactose. Let mixture (mole-ratio; about 1:1) of PENTA acetate be colorless oily matter. 5.256g was obtained.

[0062] (b) The compound 4-6 and beta-D-galactose of the synthetic above of a compound 4-7 4.238g was isolated preparatively from the mixture of PENTA acetate, it melted to 300ml of ethyl acetate, Pd-C (dry) 0.112g was added here 10%, and catalytic reduction was carried out by the ordinary pressure for 4.5 hours. It is a catalyst here. Catalytic reduction of the 0.149g was added and carried out for further 15.5 hours. The catalyst was ****(ed) and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-

hexane-ethyl-acetate 1:5), and the specified substance is considered as a colorless crystal. 1.907g was obtained.

[0063] 1 H-NMR(delta and CDCl3): 1.99 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.17 (s, 3H), 2.47 (t, 1H, J= 6.6Hz), 3.68-3.78 (m, 2H), 3.86 (t, 2H, J= 4.4Hz), 3.96 (dt, 1H, J= 1.0Hz, 6.6Hz) 4.16 (d, 2H, J= 6.6Hz), 4.52 (d, 1H, J= 8.0Hz), 5.03 (dd, 1H, J= 10.5Hz, 3.4Hz), 5.23 (dd, 1H, J= 8.0Hz, 10.5Hz), 5.40 (dd, 1H, J= 3.4Hz, 1.0Hz).

[0064] IR(KBr tab): 1753cm-1.

[0065] [alpha] D 23=-11.6 degree (c= 0.88 and CHCl3).

[0066] (c) It is about a compound 4-7 to the bottom of a synthetic argon atmosphere of a compound 4-8, 2-cyano ethyl N, N-diisopropyl chloro force FORUAMIDAITO406microl, diisopropyl ethylamine 475microl, and the mixed solution of 5ml of methylene chlorides. In addition, 0.714g was agitated at the room temperature for 1.5 hours. A solvent is distilled off under reduced pressure and it is a 2-(n-hexadecyl)-1-OKUTA decanol to a residue. 0.600g and 12ml of methylene chlorides were added and melted, and it agitated under argon atmosphere. It is a 1H-tetrazole here. 0.170g was melted to acetonitrile 5ml, in addition it agitated for 45 minutes at the room temperature. 35% hydrogen-peroxide-solution 531microl and acetonitrile 4ml were added to reaction mixture, and it agitated at the room temperature further for 1.5 hours. Chloroform is added and diluted, and it washed in this order with water, 10% citric acid, and saturation brine, and was made to dry on magnesium sulfate. A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:2), and let the specified substance be a colorless amorphous substance. 1.161g was obtained.

[0067] This thing It is the mixture of 1:1 of a diastereomer on 1 H-NMR, and some peaks were separated and observed. It converts and it is indicated that the following numbers of hydrogen become a henchman on the whole for 1 minute.

[0068] 1 H-NMR(delta and CDCl3): 0.88 (t, 6H, J= 7.0Hz), 1.22-1.34 (br s, 60H, and CH3-(CH2)15-), 1.64 (br s, 1H), 1.99 (s, 3H), 2.05 (s, 3H), 2.07 (s, 1.5H), 2.08 (1 s, 5H), 2.16 (s, 1.5H), 2.16 (s, 1.5H) 2.76-2.80 (m, 2H), 3.76-3.82 (m, 1H), 3.92 (br t, 1H), 3.98 (dd, 2H, J= 5.6Hz) 4.03-4.08 (m, 1H), 4.10-4.26 (m, 6H), 4.54 (d, 1H, J= 8.1Hz), 5.03 (dd, 1H, J= 10.3Hz, 3.4Hz), 5.20 (dd, 1H, J= 8.1Hz, 10.5Hz), 5.39-5.41 (m, 1H).

[0069] IR(KBr tab): 1749cm-1, 1232cm-1.

[0070] [alpha] D 25=-5.3 degree (c= 0.99 and CHCl3).

[0071] (d) Benzene 6ml and methanol 3ml were added and melted to the synthetic compound 4-8 of a compound 4-9, and 1.092 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated at the room temperature for 7.5 hours. It ice-cooled, and after adding 1-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. The residue was refined in the "Sephadex LH-20" column (resin; about 150ml, elution

solvent; chloroform-methanol-water 65:15:1). The water which remains is removed with azeotropy with benzene, and let the specified substance be a colorless amorphous substance. 0.752g was obtained.

[0072] 1 H-NMR(delta, CDCl3-CD3 OD 1:1): 0.89 (t, 6H, J= 7.0Hz), 1.20-1.38 (br s, 60H), 1.63 (br s, 1H), 3.51 (dd, 1H, J= 10.2Hz, 3.1Hz) 3.52 (br t, 1H), 3.58 (br t, 1H) 3.75 (dd, 1H, J= 5.4Hz, 11.5Hz), 3.81 (dd, 1H, J= 6.7Hz, 11.5Hz) 3.81-3.85 (m, 1H), 3.88 (br d, 1H), 3.91 (dd, 2H, J= 5.2Hz), 4.08 (dt, 1H, J= 11.2Hz, 4.0Hz), and 4.14-4.24 (m, 2H) and 4.29 (d, 1H, J= 7.6Hz)

[0073] [alpha] D 20=-3.4 degree (c= 1.01, CHCl3-MeOH 1:1).

[0074] FAB-MS:M;m/z=780.

[0075] Example 3 (refer to composition of a compound 4-11, and drawing 3)

(a) In addition, a compound 4-7 and 0.514 g were melted and agitated at the room temperature under a synthetic argon atmosphere of a compound 4-10 for 2 hours at 4ml of methylene chlorides to 2-cyano ethyl N, N-diisopropyl chloro force FORUAMIDAITO621microl, diisopropyl ethylamine 274microl, and the mixed solution of 1ml of methylene chlorides. A solvent is distilled off under reduced pressure and it is cetyl alcohol to a residue. 0.476g and 10ml of methylene chlorides were added and melted, and it agitated under argon atmosphere. It is a 1H-tetrazole here. In addition, 0.184g was melted and agitated at the room temperature for 1.5 hours to acetonitrile 5ml. 35% hydrogen-peroxide-solution 573microl and acetonitrile 3ml were added to reaction mixture, and it agitated at the room temperature further for 2.5 hours. Chloroform is added and diluted, and it washed in this order with water, 10% citric acid, and saturation brine, and was made to dry on magnesium sulfate. A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:3), and let the specified substance be a colorless amorphous substance. 0.277g was obtained.

[0076] This thing It is the mixture of 1:1 of a diastereomer on 1 H-NMR, and some peaks were separated and observed. It converts and it is indicated that the following numbers of hydrogen become a henchman on the whole for 1 minute.

[0077] 1 H-NMR(delta and CDCl3): 0.88 (t, 3H, J= 7.0Hz), 1.22- 1.40 (m, 26H) and 1.69 (quintet, 2H, J= 7.0Hz) -- 1.99 (s, 3H), 2.06 (s, 3H), 2.08 (s, 1.5H), 2.08 (s, 1.5H), 2.16 (s, 3H), 2.77-2.80 (m, 2H), 3.76-3.81 (m, 1H), 3.93 (dt, 1H, J= 0.9Hz, 6.8Hz), 4.04-4.26 (m, 9H), 4.54 (d, 1H, J= 8.0Hz), 5.03 (dd, 1H, J= 10.5Hz, 3.4Hz), 5.20 (dd, 0.5H, J= 8.0Hz, 10.5Hz), 5.20 (dd, 0.5H, J= 8.0Hz, 10.5Hz), and 5.39-5.41 (m, 1H).

[0078] IR(KBr tab): 1755cm-1, 1227cm-1.

[0079] [alpha] D 25=-5.3 degree (c= 0.99 and CHCl3).

[0080] (b) Benzene 4ml and methanol 2ml were added and melted to the synthetic compound 4-10 of a compound 4-11, and 0.244 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated at the

room temperature for 3.5 hours. It ice-cooled, and after adding 1-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. A residue is refined in "Sephadex LH-20" column (resin; about 100ml, elution solvent; chloroform-methanol-water 1:1), and let the specified substance be a colorless amorphous substance. 0.159g was obtained.

[0081] 1 H-NMR(delta, CDCl3-CD3 OD 1:1): 0.89 (t, 3H, J= 7.0Hz), 1.22-1.42 (m, 26H), 1.68 (quintet, 2H, J= 7.0Hz), 3.51 (dd, 1H, J= 9.5Hz, 3.2Hz) 3.52 (br t, 1H), 3.58 (br t, 1H) 3.75 (dd, 1H, J= 5.1Hz, 11.5Hz), 3.81 (dd, 1H, J= 6.6Hz, 11.5Hz) 3.81-3.85 (m, 1H), 3.88 (br d, 1H), 4.00 (dd, 1H, J= 12.9Hz), 4.07 (br dt, 1H), 4.16-4.20 (m, 2H), 4.29 (d, 1H, J= 7.6Hz).

[0082] [alpha] D 23=-1.8 degree (c= 0.55, CHCl3-MeOH 1:1).

[0083] FAB-MS:M;m/z=528.

[0084] Example 4 (refer to composition of a compound 4-13, and drawing 4)

(a) It is about a compound 4-7 to the bottom of a synthetic argon atmosphere of a compound 4-12, 2-cyano ethyl N, N-diisopropyl chloro force FORUAMIDAITO314microl, diisopropyl ethylamine 267microl, and the mixed solution of 5ml of methylene chlorides. In addition, 0.502g was agitated at the room temperature for 2 hours. A solvent is distilled off under reduced pressure and it is cholesterol to a residue. 0.742g and 10ml of methylene chlorides were added and melted, and it agitated under argon atmosphere. It is a 1H-tetrazole here. In addition, 0.179g was melted and agitated at the room temperature for 2.5 hours to acetonitrile 5ml. 35% hydrogen-peroxide-solution 560microl and acetonitrile 3ml were added to reaction mixture, and it agitated at the room temperature further for 2 hours. Chloroform is added and diluted, and it washed in this order with water, 10% citric acid, and saturation brine, and was made to dry on magnesium sulfate. A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:3), and let the specified substance be a colorless amorphous substance. 0.673g was obtained.

[0085] This thing It is the mixture of 1:1 of a diastereomer on 1 H-NMR, and some peaks were separated and observed. It converts and it is indicated that the following numbers of hydrogen become a henchman on the whole for 1 minute.

[0086] 1 H-NMR(delta and CDCl3): 0.68 (s, 3H), 0.86 (d, 3H, J= 2.2Hz), 0.87 (d, 3H, J= 2.2Hz) 0.91 (d, 3H, J= 6.6Hz), 1.02 (s, 3H), 0.90-2.10 (m, 27H), 1.99 (s, 3H), 2.06 (s, 3H), 2.08 (s, 1.5H), 2.09 (1 s, 5H), 2.16 (s, 3H), 2.45 (br d, 2H), 2.76-2.80 (m, 2H), 3.76-3.82 (m, 1H), 3.92 (dt, 1H, J= 1.1Hz, 6.7Hz), 4.04-4.08 (m, 1H), 4.11-4.28 (m, 7H), 4.54 (d, 0.5H, J= 8.1Hz) 4.54 (d, 0.5H, J= 8.1Hz), 5.02 (dd, 0.5H, J= 10.5Hz, 3.4Hz) 5.03 (dd, 0.5H, J= 10.5Hz, 3.4Hz), 5.20 (dd, 0.5H, J= 8.1Hz, 10.3Hz), 5.21 (dd, 0.5H, J= 8.1Hz, 10.3Hz), 5.39-5.41 (m, 2H).

[0087] IR(KBR tab): 1753cm-1, 1227cm-1.

[0088] [alpha] D 25=-20.1 degree (c= 1.00 and CHCl3).

[0089] (b) Benzene 6ml and methanol 3ml were added and melted to the synthetic compound 4-12 of a compound 4-13, and 0.634 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated at the room temperature for 5.5 hours. It ice-cooled, and after adding 2-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. A residue is refined in "Sephadex LH-20" column (resin; about 100ml, elution solvent; chloroform-methanol 1:1), and let the specified substance be a colorless amorphous substance. 0.427g was obtained.

[0090] 1 H-NMR(delta, CDCl3-CD3 OD 4:3): 0.70 (s, 3H), 0.87 (d, 3H, J= 2.2Hz) 0.88 (d, 3H, J= 2.0Hz), 0.93 (d, 3H), 1.03 (s, 3H), 0.90-2.06 (m, 26H), 2.39-2.47 (m, 2H), 3.51 (dd, 1H, J= 10.0Hz, 3.0Hz), 3.52 (br t, 1H), 3.58 (br t, 1H), 3.75 (dd, 1H, J= 5.4Hz, 11.5Hz), 3.82 (dd, 1H, J= 6.6Hz, 11.5Hz) 3.80-3.84 (m, 1H), 3.88 (br d, 1H), 4.07 (br dt, 1H), 4.10-4.22 (m, 4H), 4.29 (d, 1H), J= 7.5Hz, and 5.40 (br d, 1H).

[0091] [alpha] D 23=-21.7 degree (c= 1.00, CHCl3-MeOH 1:1).

[0092] FAB-MS:M;m/z=672.

[0093] Example 5 (refer to composition of a compound 4-19, and drawing 5)

(a) Synthetic sodium hydride of a compound 4-14 Washed 3.300g (60% dispersion) by n-hexane, 10ml of N.N-dimethylformamide was made to suspend, and it agitated under ice-cooling. It is 2 and 2-dimethyl here. - 1, 3-dioxolane-4-methanol In addition, 9.891g was melted and agitated for 10 minutes at the room temperature to 15ml of N.N-dimethylformamide. Here, 35ml of N.N-dimethylformamide was added and it agitated for 20 more minutes. It ice-cooled again, benzyl bromide 9.35ml was added, and it agitated at the room temperature for 11.5 hours. The solvent was distilled off under reduced pressure. Ethyl acetate was added to the residue, insoluble matter was ****(ed), and the solvent was distilled off under reduced pressure. The silica gel column chromatography refined the residue (elution solvent; n-hexane-ethyl-acetate 10:1), and it was obtained 12.029g, having used the specified substance as light yellow oily matter.

[0094] 1 H-NMR(delta and CDCl3): 1.37 (s, 3H), 1.42 (s, 3H), 3.48 (dd, 1H, J= 9.8Hz, 5.5Hz) 3.56 (dd, 1H, Jm =9.8Hz, 5.5Hz, CH2 OBn), 3.75 (dd, 1H, J= 8.3Hz, 6.3Hz) 4.06 (dd, 1H, J= 8.3Hz, 6.3Hz), 4.30 (br tt, 1H), 4.56 (d, 1H, J= 12.2Hz), 4.60 (d, 1H, J= 12.2Hz), and 7.27-7.37 (m, 5H).

[0095] (b) Methanol 30ml was added and melted to the synthetic compound 4-14 of a compound 4-15, and 12.018g. 5ml of 2-N hydrochloric acids was added here, and it agitated for 40 minutes at the room temperature. The solvent was distilled off under reduced pressure and the remaining water was removed with azeotropy with benzene. A silica gel column chromatography refines a residue (elution solvent; ethyl acetate), and let the specified substance be colorless oily matter. 8.314g was obtained.

[0096] 1 H-NMR(delta and CDCl3): 2.14 (br t, 1H), 2.64 (d, 1H, J= 5.1Hz) 3.55 (dd, 1H, J= 9.6Hz, 6.2Hz), 3.59 (dd, 1H, J= 9.6Hz, 4.0Hz) 3.64 (ddd, 1H, J= 11.2Hz, 5.6Hz), 3.71 (ddd, 1H, J= 11.2Hz, 3.9Hz, 7.2Hz), 3.87-3.92 (m, 1H), 4.56 (d, 1H, J= 12.2Hz), 7.29-7.38 (m, 5H).

[0097] (c) Synthetic sodium hydride of a compound 4-16 Washed 1.891g (60% dispersion) by n-hexane, 20ml of N.N-dimethylformamide was made to suspend, and it agitated under ice-cooling. In addition, a compound 4-15 and 3.915 g were melted and agitated for 40 minutes at the room temperature here at 20ml of N.N-dimethylformamide. It ice-cooled again, 1-BUROMO hexadecane 15.8ml was added, and it agitated at 70 degrees C for 16 hours. The solvent was distilled off under reduced pressure. Ethyl acetate was added to the residue, insoluble matter was ****(ed), and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 25:1), and let the specified substance be colorless oily matter. 4.733g was obtained.

[0098] 1 H-NMR(delta and CDCl3): 0.88 (t, 6H, J= 7.0Hz), 1.22-1.34 (m, 52H), 1.51-1.59 (m, 4H), 3.43 (t, 2H, J= 6.6Hz), 3.46-3.61 (m, 5H), 3.57 (t, 2H, J= 6.6Hz), 4.55 (s, 2H), and 7.27-7.33 (m, 5H).

[0099] (d) 60ml [of ethyl acetate] and methanol 20ml was added and melted to the synthetic compound 4-16 of a compound 4-17, and 4.641 g. It is 10% here. Pd-C (dry) 0.197g was added and it returned by the ordinary pressure for 4.5 hours. The specified substance which added the methylene chloride and deposited was melted, the catalyst was ****(ed), and the solvent was distilled off under reduced pressure. Let the specified substance be colorless powder. 3.704g was obtained.

[0100] 1 H-NMR(delta and CDCl3): 0.88 (t, 6H, J= 7.0Hz), 1.22-1.34 (m, 52H), 1.52-1.61 (m, 4H), 2.16 (br t, 1H), 3.42-3.55 (m, 6H), 3.58-3.64 (m, 2H), and 3.70-3.74 (m, 1H).

[0101] (e) It is about a compound 4-7 to the bottom of a synthetic argon atmosphere of a compound 4-18, 2-cyano ethyl N, N-diisopropyl chloro force FORUAMIDAITO293microl, diisopropyl ethylamine 343microl, and the mixed solution of 3ml of methylene chlorides. In addition, 0.515g was agitated for 30 minutes at the room temperature. A solvent is distilled off under reduced pressure and it is about a compound 4-17 to a residue. 0.710g, 5ml [of methylene chlorides], and acetonitrile 5ml was added (it does not melt completely), and it agitated under argon atmosphere. It is a 1H-tetrazole here. 0.138g was melted to acetonitrile 5ml, and, in addition, the ultrasonic wave was applied for 30 minutes at the room temperature. 10ml of methylene chlorides was added and melted here, and it agitated for 40 minutes at the room temperature. 35% hydrogen-peroxide 575microl and acetonitrile 2ml were added to reaction mixture, and it agitated at the room temperature further for 2.5 hours. Chloroform is added and diluted, and it washed in this order with water, 10% citric acid, and saturation brine, and was made to dry on magnesium sulfate. A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:2), and let the specified substance be a colorless amorphous substance. 0.636g was obtained.

[0102] This thing It of four sorts of diastereomers was also considered to be the mixture of every equivalence on 1 H-NMR, and some peaks were separated and observed. It converts and it is indicated that the following hydrogen number becomes a henchman on the whole for 1 minute.

[0103] 1 H-NMR(delta and CDCl3): 0.88 (t, 6H, J= 7.0Hz), 1.22-1.33 (m, 52H), 1.52-1.58 (m, 4H), 1.99 (s, 3H), 2.06 (s, 3H), 2.08 (s, 1.5H), 2.09 (s, 1.5H), 2.16 (s, 3H), 2.76-2.80 (m, 2H), 3.42-3.63 (m, 7H), 3.76-3.82 (m, 1H), 3.93 (br t, 1H) 4.02-4.29 (m, 9H), 4.54 (d, 0.25H, J= 8.0Hz) 4.54 (d, 0.5H, J= 8.0Hz), 4.55 (d, 0.25H, J= 8.0Hz), 5.03 (dd, 1H, J= 10.5Hz, 3.3Hz), 5.20 (dd, 1H, J= 8.0Hz, 10.5Hz), 5.39-5.40 (m, 1HH).

[0104] IR(KBr tab): 1753cm-1, 1227cm-1.

[0105] [alpha] D 26=-5.7 degree (c= 1.04 and CHCl3).

[0106] (f) Benzene 5ml and methanol 3ml were added and melted to the synthetic compound 4-18 of a compound 4-19, and 0.605 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated at the room temperature for 2.5 hours. It ice-cooled, and after adding 2-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. the water which refines a residue in "Sephadex LH-20" column (resin; about 150ml, elution solvent; chloroform-methanol-water 65[:] :15:1), and remains -- azeotropy with benzene -- removing -- the specified substance -- colorlessness -- being amorphous -- carrying out -- 0.450g was obtained.

[0107] 1 H-NMR(delta, CDCl3-CD3 OD 4:3): 0.89 (t, 6H, J= 7.0Hz), 1.23-1.38 (m, 52H), 1.58 (br quintet, 4H), 3.45-3.68 (m, 9H), 3.76 (dd, 1H, J= 5.2Hz, 11.6Hz), 3.82 (dd, 1H, J= 6.6Hz, 11.6Hz) 3.80-3.84 (m, 1H), 3.88 (br d, 1H), 3.99-4.04 (m, 1H), 4.04-4.10 (m, 2H), 4.16-4.22 (m, 2H), 4.29 (d, 1H, J= 7.6Hz).

[0108] [alpha] D 23=-3.4 degree (c= 1.01, CHCl3-MeOH 1:1).

[0109] FAB-MS:M;m/z=826.

[0110] Example 6 (refer to composition of a compound 4-24, and drawing 6)

(a) Synthetic sodium hydride of a compound 4-20 Washed 4.421g (60% dispersion) by n-hexane, 100ml of N.N-dimethylformamide was made to suspend, and it agitated under ice-cooling. Diethylene-glycol 9.49ml was added here and it agitated at the room temperature for 1 hour. Benzyl bromide 11.9ml was added and it agitated at the room temperature for 11 hours. The solvent was distilled off under reduced pressure. The silica gel column chromatography refined the residue (elution solvent; n-hexane-ethyl-acetate 1:2), and it was obtained 10.432g, having used the specified substance as light yellow oily matter.

[0111] 1 H-NMR(delta and CDCl3): 2.36 (t, 1H, J= 6.2Hz), 3.61-3.66 (m, 4H), 3.69-3.71 (m, 2H), 3.72-3.75 (m, 2H), 4.58 (s, 2H), 7.27-7.38 (m, 5H).

[0112] (b) Synthetic beta-D-galactose of a compound 4-21 PENTA acetate It is about a compound 4-20 to 4.597g. 3.005g and 50ml of methylene chlorides were added and melted, little "molecular-sieve 4A" was added, and it agitated at the room temperature for 2 hours. This was ice-cooled, and, in addition, 5.79ml of boron-trifluoride diethylether complexes was melted and agitated at the room temperature for 12 hours to 10ml of methylene chlorides. Insoluble matter was ****(ed), it diluted with the

methylene chloride, and saturation brine washed 6 times. The organic layer was dried on magnesium sulfate and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 3:2), and they are the specified substance and a beta-D-galactose. Let mixture (mole-ratio; about 10:1) of PENTA acetate be colorless oily matter. 3.209g was obtained. In addition, a part of following physical-properties values were measured with the sample obtained in the pure form.

[0113] 1 H-NMR(delta and CDCl3): 1.99 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 3.60-3.68 (m, 6H), 3.77 (ddd, 1H, J= 11.1Hz, 4.0Hz, 7.1Hz), 3.87 (br dt, 1H) 3.96 (dt, 1H, J= 11.1Hz, 4.3Hz), 4.12 (dd, 1H, J= 6.8Hz, 11.2Hz) 4.16 (dd, 1H, J= 6.6Hz, 11.2Hz), 4.57 (s, 2H), 4.57 (d, 1H, J= 8.1Hz), 5.00 (dd, 1H, J= 10.5Hz, 3.4Hz), 5.21 (dd, 1H, J= 8.1Hz, 10.5Hz), 5.37 (dd, 1H, J= 3.4Hz, 1.1Hz).

[0114] IR(KBr tab): 1753cm-1.

[0115] [alpha] D 22=-7.3 degree (c= 0.95 and CHCl3).

[0116] (c) The compound 4-21 and beta-D-galactose of the synthetic above of a compound 4-22 Mixture of PENTA acetate 3.174g was melted to 50ml of ethyl acetate, Pd-C (dry) 0.155g was added here 10%, and catalytic reduction was carried out by 50 psi for 16.5 hours. The catalyst was ****(ed) and the solvent was distilled off under reduced pressure. A silica gel column chromatography refines a residue (elution solvent; n-hexane-ethyl-acetate 1:5), and let the specified substance be a colorless amorphous substance. 2.093g was obtained.

[0117] 1 H-NMR(delta and CDCl3): 1.99 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.16 (s, 3H), 2.26 (t, 1H, J= 6.2Hz), 3.55-3.78 (m, 7H), 3.92 (br dt, 1H), 3.97-4.00 (m, 1H), 4.13 (dd, 1H, J6a=6.8Hz, J= 11.2Hz), 4.19 (dd, 1H, J= 6.8Hz, 11.2Hz) 4.57 (d, 1H, J= 7.8Hz), 5.03 (dd, 1H, J= 10.3Hz, 3.4Hz), 5.23 (dd, 1H, J= 8.1Hz, 10.5Hz), and 5.40 (dd, 1H, J= 3.4Hz, 1.0Hz).

[0118] IR(KBr tab): 1749cm-1.

[0119] [alpha] D 22=-6.7 degree (c= 1.01 and CHCl3).

[0120] (d) It is about a compound 4-22 to the bottom of a synthetic argon atmosphere of a compound 4-23, 2-cyano ethyl N, N-diisopropyl chloro force FORUAMIDAITO302microl, diisopropyl ethylamine 295microl, and the mixed solution of 1ml of methylene chlorides. In addition, 0.493g was agitated at the room temperature for 3 hours. A solvent is distilled off under reduced pressure and it is a 2-(n-hexadecyl)-1-OKUTA decanol to a residue. 0.373g and 10ml of methylene chlorides were added and melted, and it agitated under argon atmosphere. It is a 1H-tetrazole here. 0.158g was melted to acetonitrile 8ml, and in addition, the ultrasonic wave was applied for 10 minutes and it agitated at the room temperature further for 20 hours. 35% hydrogen-peroxide-solution 330microl and acetonitrile 2ml were added to reaction mixture, and it agitated at the room temperature further for 6.5 hours. Chloroform is added and diluted, and it washed in this order with water, 10% citric acid, and saturation brine, and was made to dry on magnesium sulfate. A solvent is distilled off under reduced pressure, and a silica gel column chromatography refines a

residue (elution solvent; n-hexane-ethyl-acetate 1:2), and let the specified substance be a colorless amorphous substance. 0.593g was obtained.

[0121] This thing It is the mixture of 1:1 of a diastereomer on 1 H-NMR, and some peaks were separated and observed. It converts and it is indicated that the following hydrogen number becomes a henchman on the whole for 1 minute.

[0122] 1 H-NMR(delta and CDCl3): 0.88 (t, 6H, J= 7.0Hz), 1.22-1.34 (br s, 60H), 1.64 (br s, 1H), 1.99 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.16 (s, 1.5H), 2.16 (s, 1.5H), 2.74-2.84 (m, 2H), 3.66-3.76 (m, 5H), 3.90-3.94 (m, 1H), 3.96-4.00 (m, 1H), 3.99 (dd, 2H, J= 5.5Hz), 4.13 (dd, 1H, J= 7.0Hz, 11.5Hz) 4.18 (dd, 1H, J= 6.3Hz, 11.5Hz), 4.19-4.28 (m, 4H), 4.55 (d, 0.5H, J= 8.1Hz), 4.56 (d, 0.5H, J= 8.1Hz), 5.03 (dd, 0.5H, J= 10.5Hz, 3.2Hz), 5.03 (dd, 0.5H, J= 10.5Hz, 3.2Hz), and 5.39 (dd, 1H, J= 3.2Hz, 1.0Hz).

[0123] IR(KBr tab): 1753cm-1, 1229cm-1.

[0124] [alpha] D 25=-4.9 degree (c= 0.96 and CHCl3).

[0125] (e) Benzene 6ml and methanol 3ml were added and melted to the synthetic compound 4-23 of a compound 4-24, and 0.556 g. The sodium-methoxide methanol solution was added here 28%, and it was referred to as pH=10, and agitated at the room temperature for 2.5 hours. It ice-cooled, and after adding 1-N hydrochloric acid and being referred to as pH=1, the solvent was distilled off under reduced pressure. The residue was refined in the "Sephadex LH-20" column (resin; about 150ml, elution solvent; chloroform-methanol 1:1). The water which remains is removed with azeotropy with benzene, and let the specified substance be a colorless amorphous substance. 0.394g was obtained.

[0126] 1 H-NMR(delta, CDCl3-CD3 OD 1:1): 0.89 (t, 6H, J= 7.0Hz), 1.20-1.38 (br s, 60H), 1.64 (br s, 1H), 3.50-3.53 (m, 2H), 3.58 (br t, 1H), 3.72-3.82 (m, 7H), 3.89 (br d, 1H), 3.91 (dd, J= 5.4Hz), 4.02-4.06 (m, 1H), 4.11-4.15 (m, 2H), 4.29 (d, 1H, J= 7.6Hz).

[0127] [alpha] D 20=-2.2 degree (c= 0.99, CHCl3-MeOH 1:1).

[0128] FAB-MS:M;m/z=824.

[0129] Example 7 (manufacture of a liposome)

L-alpha-dipalmitoyl phosphatidylcholine 80micromol, cholesterol 80micromol and a compound 4-9, and 16micromol It melted to the mixture (volume ratio 1:1) of chloroform and a methanol. Next, the organic solvent was removed in the nitrogen gas air current, and the glass wall of a centrifugation tube was made to generate a lipid film.

[0130] The phosphoric-acid buffer-ized physiological saline of 1mM inulin which contains 3H-inulin 5.29MBq (160microcurie) beforehand warmed at 45 degrees C here (pH 7.4.) It shook having added hereafter 8ml which may be abbreviated to PBS, and keeping it warm at about 50 degrees C, it ultrasonicated still more lightly, and the suspension of a liposome was prepared. This was warmed at 60 degrees C, the

polycarbonate nature membrane filter which has an aperture (0.2 micrometers, 0.1 micrometers, and 0.08 micrometers) was passed in order, and the suspension of a liposome with a particle size of about 0.1 micrometers was prepared.

[0131] Next, ultra-centrifugal separation of this was carried out 3 times (for the 1st time, 14 hours and 2 and the 3rd time are 2 hours at 105 xg in 105 xg), the inulin which was not held by removing supernatant liquor at a liposome was removed, PBS was added, and one sort of liposome suspension of 6ml of whole quantity was obtained.

[0132] Moreover, the liposome suspension of 6ml of whole quantity was obtained like the above without blending a compound. This was made into the control liposome.

[0133] The example 1 (medicine delivery ability of a liposome) of inspection

b. It is [about two sorts of samples prepared in the test-method example 7] 5micromol as the sum total of an L-alpha-dipalmitoyl phosphatidylcholine and cholesterol per weight of 100g from the hind-foot vein of SD system male rat (weights 200-250g), respectively. It poured in.

[0134] About 0.2ml collected blood blood from ****** in after [medication] 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, and the 6th hour, 0.1ml of after [centrifugal] plasma was placed on the filter paper, and it burned in the burner after dryness, and asked for the radioactivity depending on the method of liquid scintillation. Moreover, the rat was slaughtered after medication in the 6th hour, each about 200mg of various organizations was taken, and it burned in the burner after dryness, asked for the radioactivity depending on the method of liquid scintillation, and asked for the inulin concentration per 1g of each internal organs.

[0135] b. As shown in a result and consideration drawing 7 , to control, the concentration in plasma fell quickly, the concentration in liver increased notably, and the liposome embellished with the compound of this invention became clear [piling up liver].

[0136]

[Effect of the Invention] The place where the outstanding liposome in which it contains such phospholipid if the new phospholipid which was excellent as a material which gives internal-organs directivity to a liposome with this invention is a total is offered easily came.
